Remarks

Claims 14-46 are pending in the subject application. By this Amendment, Applicants have canceled claims 24-28, 30, 31, and 35-45 and amended claims 14, 20, 21, 22, 29, and 34. Support for the amendments can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 14-23, 29, 32-34, and 46 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

As an initial matter, Applicants gratefully acknowledge the Examiner's indication that claims 23, 32, and 33 are objected to but would be allowable if rewritten into independent form to include the limitations of any base and intervening claims. Applicants also gratefully acknowledge the Examiner's withdrawal of the objections to the specification and certain of the rejections under 35 U.S.C. § 112, second paragraph.

Applicants note that the priority issue raised in the previous Office Action has been withdrawn in view of the previous response filed in this matter. Applicants request that a corrected Filing Receipt be issued in this matter that properly sets forth the priority claim for this application.

Claims 14-20 remain rejected and claims 21, 22, 24-31, and 34-46 have been rejected under 35 U.S.C. § 112, first paragraph, on the basis that the specification, while enabling for SEQ ID NOs: 1 and 3, in that they encode a protein that binds g34872, does not reasonably provide enablement for variants, analogs, or derivatives of SEQ ID NOs: 1 and 3 which are at least 18 nucleotides in length.

The Office Action argues that the as-filed specification fails to enable the claimed invention on the basis that it fails to describe other sequences or variants that are capable of binding to the g34872 protein. The Office Action further argues that the enabled use and utility of the claimed polypeptides is that they encode the PAPAP protein of SEQ ID NO: 2 which is shown to bind the g34872 protein that has been implicated in schizophrenia. The Office Action further indicates that the disclosure fails to identify which portions of the protein are critical for its interaction with the g34782 protein; what modifications one can make to the sequences of SEQ ID NO: 1 and 3 that will result in the same binding property as the polypeptide of SEQ ID NO: 2; and guidance as to how one should use the variants of the polynucleotides set forth in SEQ ID NO: 1 and 3 or the proteins

encoded thereby that do not bind to the g34872 protein. The Office Action further argues that certain amino acid residues are critical to structure/function and in providing correct three-dimensional spatial orientation of binding and active sites to various regions of the protein. The Office Action cites a variety of references in support of its position. Applicants respectfully traverse.

Applicants respectfully submit that the Patent Office appears to have taken too narrow a view of the claimed polynucleotides and the polypeptides encoded thereby. In addition to binding g34872, the specification indicates that the polypeptide of SEQ ID NO: 2 has homology to calcium/calmodulin-dependent kinase II inhibitors [CaM-KIIN] (see specification at page 55, lines 15-25) and the polypeptide of SEQ ID NO: 2 can be used to bind to the g34872 polypeptide or a calcium/calmodulin-dependent kinase II (CaM-KII) (see page 96, lines 3-4). The specification also teaches certain immunogenic epitopes of the PAPAP polypeptide (SEQ ID NO: 2) at pages 62-63. Finally, Applicants submit that the claims now recite polynucleotides that encode a polypeptide that is at least 95% identical to the amino acid sequence of SEQ ID NO: 2 (*e.g.*, a polypeptide that contains between one and four amino acid substitutions over the full length of the polypeptide).

As set forth in the specification at page 55, the polypeptide of SEQ ID NO: 2 has homology to the polypeptide having GenBank Accession Number AF271156.1. At the nucleic acid level, there is 90.8% identity between the PAPAP encoding nucleic acid and the nucleic acid associated with AF271156.1. The PAPAP polypeptide exhibits about 92.3% identity to the polypeptide identified in AF271156.1. For the convenience of the Examiner, an alignment of these sequences is attached to this response. CaM-KIIN polypeptides were known in the art prior to the effective filing date of the subject invention. For example, Chang *et al.* (*Proc. Nat'l. Acad. Sci. USA*, 1998, 95:10890-10895) teach the characterization of a CaM-KIIN. Chang *et al.* further teach a 27 amino acid domain (referred to as CaM-KIINtide) that is identified as responsible for the inhibition of CaM-KII. The domain was identified via truncation of the polypeptide at the carboxyl-terminus (see page 10893, column 1, lines 8-15 and Figure 1). As noted in the reference, inhibitory potency resided largely in 28 residues near the COOH terminus of the polypeptide[1]. For the convenience of the Examiner,

[1] Applicants note that a typographical error appears to exist in this passage as a 27 amino acid segment is underlined in Figure 1 and identified in the section discussing the CaM-KIINtide.

Applicants have converted the amino acid sequence of SEQ ID NO: 2 into single letter code and have underlined/bolded the domain that corresponds to the inhibitory domain identified by Chang *et al.* As the Patent Office will note, the polypeptide of SEQ ID NO: 2 contains the inhibitory domain identified in Chang *et al.* at about the same location as that identified in the CaM-KIIN of Chang *et al.*

SEQ ID NO: 2

MWEVLPYGDEKLSPYGDGGDVGQIFSCRLQDTNNFFGAGQN**KRPPKLGQIGRSKR VVIEDDRIDDVLK**NMTDKAPLVSNSPKTMS

Accordingly, Applicants respectfully submit that, in view of the state of the art, that one skilled in the art would have recognized those sections of SEQ ID NO: 2 that could be modified via substitution of up to four amino acids without affecting the ability of the polypeptide to inhibit CaM-KII. Applicants further submit that the Patent Office has not established that the combination of the disclosure of the specific chemical structures of a polynucleotide comprising the coding sequence set forth in SEQ ID NOs: 1 or 3, as well as teachings in the specification on how to test for CaM-KIIN or g34872 binding activity and recognition in the art as to the areas of polypeptides similar to SEQ ID NO: 2 that could be altered without affecting, for example, CaM-KIIN binding, are insufficient to enable a polynucleotide having at least 95% identity to the entire coding region of SEQ ID NOs: 1 or 2 or a polynucleotide encoding a polypeptide that is 95% identical to the polypeptide of SEQ ID NO: 4. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Applicants further submit that the as-filed specification also provides guidance as to those segments of SEQ ID NO: 2 that serve as antigenic regions of the polypeptide. As discussed at page 62, positions 8-11; 31-33; 40-47; 51-54; 59-62; and 80-83 correspond to immunogenic epitopes of the PAPAP polypeptide. In view of such teachings, one skilled in the art would recognize that up to four amino acid substitutions could be made over the length of the polypeptide at various locations without necessarily affecting the immunogenicity of a given epitope of the PAPAP polypeptide. For example, up to four consecutive amino acid changes could be introduced at positions 2-5 of the polypeptide that would not reasonably be expected to affect epitopes located towards the carboxyl terminus of the polypeptide. Accordingly, Applicants respectfully submit that the claimed invention

is enabled by the as-filed specification and that one skilled in the art would be able to practice the invention without undue experimentation.

Finally, Applicants note that the Office Action argues that no guidance has been provided as to how one should use the variants of the polynucleotides set forth in SEQ ID NO: 1 and 3 or the proteins encoded thereby that do not bind to the g34872 protein. Applicants respectfully submit that there is no statutory requirement for teaching how one is to make or use variants of the polynucleotides or proteins encoded thereby that do not bind to the g34872 polypeptide. To the extent that this aspect of the rejection is directed to the possible existence of non-operational embodiments within the scope of the claims, Applicants respectfully submit that this does not necessarily mean the claims are unpatentable. *Texas Instruments v. U.S. International Trade Commission*, 805 F.2d 1558, 1562, 231 U.S.P.Q. 833, 835 (Fed. Cir 1986). "Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid.... [I]f the number of inoperative combinations becomes significant, and in effect forces one of ordinary in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid." *EMI Group North America Inc. v. Cypress Semiconductor Corp.*, 60 USPQ2d 1423 (CA FC 2001); *Atlas Powder Co. v. E.I. Du Pont De Nemours Co.*, 750 F.2d 1569, 1576-77, 224 U.S.P.Q. 409, 414(Fed. Cir. 1984).

In this case, Applicants again respectfully submit that the specification specifically describes the chemical structures of a polynucleotide that encode the PAPAP polypeptide of SEQ ID NO: 2 (see, for example SEQ ID NO: 1 or 3). Further, the specification provides an example of how to screen for interaction between PAPAP polypeptides and g34872 (see Example 1) and the claims and the specification indicate that variants retain the biological activities associated with the PAPAP polypeptide (*e.g.*, the ability to bind to the g34872 polypeptide or the ability to bind/localize CaM-KII polypeptides (page 95, line 8 through page 96, line 4)). While a large number of variants may be tested in order to identify those having the biological activity recited within the claims, such testing does not amount to undue experimentation. As the Patent and Trademark Office Board of Patent Appeals and Interferences has stated: "The test [for enablement] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification

in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed". *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (1982). Accordingly, in view of the teachings or the specification and the level of skill in this area of art, it is respectfully submitted that one skilled in the art would have been able to identify variant polynucleotides within the scope of the claims and that undue experimentation would not have been required to practice the invention.

Claims 14-20 stand rejected under 35 U.S.C. § 112, first paragraph as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art at the time the application was filed that the inventor had possession of the claimed invention. The Office Action argues that the claims recite polynucleotides that encode polypeptides that are at least 70% identical to the amino acid sequence of SEQ ID NO: 2, polynucleotides which will hybridize under stringent conditions to the polynucleotides of SEQ ID NOs: 1 and 3 and polynucleotides that encode proteins that are at least 70% identical to the amino acid sequence of SEQ ID NO: 2, and polynucleotides that hybridize to or are variants, fragments, analogs, or derivatives of the polynucleotides of SEQ ID NOs: 1 and 3 and polynucleotides that encode proteins that are at least 70% identical to the amino acid sequence of SEQ ID NO: 2. The Office Action also argues that, with the exception of the sequences referred to above (SEQ ID NOs: 1 or 3), the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides and DNA molecules, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation.

The Enzo court stated that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.'" See *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316,1324, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002) (emphasis omitted, bracketed material in original).

In this case, the specification specifically describes the chemical structures of a polynucleotide that encodes a polypeptide of SEQ ID NO: 2 and a polynucleotide comprising the coding sequence set forth in SEQ ID NOs: 1 or 3. Contrary to the examiner's position, it would reasonably appear that such a description in the specification would constitute sufficiently detailed, relevant identifying characteristics of the claimed subject matter consistent with the holdings set forth in Enzo (*supra*). Applicants further submit that the examiner has failed to indicate why one of ordinary skill in the art, who is in possession of the very specific chemical structures of a polynucleotide that encodes a polypeptide of SEQ ID NO: 2 and a polynucleotide comprising the coding sequence set forth in SEQ ID NO: 1, would be unable to recognize, upon reading the disclosure, that appellants invented the claimed subject matter, including polynucleotides having homologues sharing structural features with the specifically claimed and disclosed structures. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claims 14-20 remain rejected and claims 21-46 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. The Office Action rejects the claims on the basis that there is no limiting definition related to "stringent hybridization conditions" within the specification and because of the recitation of the term "variant". Applicants respectfully submit that these issues are now moot in view of the cancellation of the claims. The Examiner indicates that the recitation of "a polynucleotide of SEQ ID NO: 1" is indefinite in the use of the article "a." Claim 21 has been amended to substitute the word "a" with "the." Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claims 14-20 remain rejected under 35 U.S.C. § 102(e) as anticipated by Kaser *et al.* (U.S. Patent No. 6,222,027). The Office Action indicates that the Kaser *et al.* patent teaches a nucleic acid that is expressed in the hippocampus that shares 100% sequence similarity to nucleotides 685-1058 of SEQ ID NO: 1. Applicants respectfully assert that the Kaser *et al.* patent does not anticipate the claimed invention in that it fails to teach a polynucleotide fragment that is at least 500 contiguous nucleotides in length or that hybridizes to SEQ ID NO: 1, 3 or the complements thereof and which is

at least 500 contiguous nucleotides in length. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(e) is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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FCE/sl
Attachment: Sequence Alignment

PAPAP-AF271156_prot_alignment.doc

```
CLUSTAL W (1.83) Multiple Sequence Alignments


Sequence format is Pearson
Sequence 1: US692_SEQ_ID_NO02        85 aa
Sequence 2: AF271156                 78 aa
Unknown OUTPUT type: aln

Start of Pairwise alignments
Aligning...

Sequences (1:2) Aligned. Score: 92.3077
Sequences (2:2) Aligned. Score: 100
Guide tree        file created:   [seqfile_1728905.dnd]
Start of Multiple Alignment
There are 1 groups
Aligning...
Group 1: Sequences:   2      Score:1624
Alignment Score 440
CLUSTAL-Alignment file created  [seqfile_1728905.aln]
```

Clustalw *.aln format:

```
CLUSTAL W (1.83) multiple sequence alignment


US692_SEQ_ID_NO02       MWEVLPYGDEKLSPYGDGGDVGQIFSCRLQDTNNFFGAGQNKRPPKLGQIGRSKRVVIED
AF271156                MSFVLPYGDEKLSPYGDGGDVGQIFSCRLQDTNNFFGAGQSKRPPKLGQIGRSKRVVIED
                        * ********************************.*********************

US692_SEQ_ID_NO02       DRIDDVLKNMTDKAPLVSNSPKTMS
AF271156                DRIDDVLKTMTDKAP-----PGV--
                        *********.******      * .
```

```
SIM - Results of the Alignment of 2 Nucleic Acid Sequences
Results of SIM with:
Sequence 1: US692_SEQ_ID_NO01, (1104 residues)
Sequence 2: AF271156, (409 residues)

using the parameters:
Number of alignments computed: 20
Cost of a matching aligned pair: 1
Cost of a transition: -1
Cost of a transversion: -1
Gap open penalty: 6.0
Gap extension penalty: 0.2

--------------------------------------------------------------------------------

90.8% identity in 390 residues overlap; Score: 297.6; Gap frequency: 3.1%

US692_SEQ_     78 GACGCGACCATGTGGGAGGTGCTGCCCTACGGCGACGAGAAGCTGAGCCCCTACGGCGAC
AF271156,       1 GACGCGACCATGTCCGAGGTGCTGCCCTACGGCGACGAGAAGCTGAGCCCCTACGGCGAC
                  ************* ************************************************

US692_SEQ_    138 GGCGGCGACGTGGGCCAGATCTTCTCCTGCCGCCTGCAGGACACCAACAACTTCTTCGGC
AF271156,      61 GGCGGCGACGTGGGCCAGATCTTCTCGTGCCGCCTGCAGGACACCAACAACTTCTTCGGC
                  ********************************** ************************************

US692_SEQ_    198 GCCGGGCAGAACAAGCGGCCGCCCAAGCTGGGCCAGATCGGCCGGAGCAAGCGGGTTGTT
AF271156,     121 GCCGGGCAGAGCAAGCGGCCGCCCAAGCTGGGCCAGATCGGCCGGAGCAAGCGCGTTGTT
                  ********** ****************************************** ******

US692_SEQ_    258 ATTGAAGATGATAGGATTGATGACGTGCTGAAAAATATGACCGACAAGGCACCTC-TGGT
AF271156,     181 ATTGAAGATGATAGGATCGATGACGTGCTCAAAACCATGACCGACAAGGCACCTCCTGGT
                  ********************** ***************** ******************** ****

US692_SEQ_    317 GTCTAACT--CCCCAAAGACAATGAGTTAAGGGAGAGAATAGGAAC-------GGCGGTA
AF271156,     241 GTCTAACTGCCCCCAAAGACAATGTGTTGAGGGAAGGAATAAGAAGAGTGGCGGGCTGTG
                  ******** ************** *** ***** ***** ***         *** **

US692_SEQ_    368 ACAGTTATTGGCAAAAAGCATGAAAAG-AGAAAGCACTTTGAAATTTATTACTAGCTTG-
AF271156,     301 ACAGTTACTGACAAAAAGCATGAGGAGGAGAAAGCACTTTGGAATTTATTATTAGCTTGC
                  ******* ** ************  ** ************ ********* *******

US692_SEQ_    426 TACCCACGATGAAATCAACAACCTGTATCT
AF271156,     361 TACCTACGATGAAATCGACAACCTGTGTCT
                  **** *********** ********* ***

--------------------------------------------------------------------------------73.5%
identity in 34 residues overlap; Score: 16.0; Gap frequency: 0.0%

US692_SEQ_     17 GCTGACCCTGTCCGCCGCGGGCGGGGACGCGGGC
AF271156,      42 GCTGAGCCCCTACGGCGACGGCGGCGACGTGGGC
                  ***** **  * ** **  ***** **** ****

--------------------------------------------------------------------------------
100.0% identity in 13 residues overlap; Score: 13.0; Gap frequency: 0.0%

US692_SEQ_    102 CCCTACGGCGACG
AF271156,      49 CCCTACGGCGACG
                  *************
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--------------------------------------------------------------------------------
100.0% identity in 13 residues overlap; Score: 13.0; Gap frequency: 0.0%

US692_SEQ_    126 CCCTACGGCGACG
AF271156,      25 CCCTACGGCGACG
                  *************

--------------------------------------------------------------------------------87.5%
identity in 16 residues overlap; Score: 12.0; Gap frequency: 0.0%

US692_SEQ_    236 CGGCCGGAGCAAGCGG
AF271156,     123 CGGGCAGAGCAAGCGG
                  *** * **********

--------------------------------------------------------------------------------
100.0% identity in 11 residues overlap; Score: 11.0; Gap frequency: 0.0%

US692_SEQ_    226 TGGGCCAGATC
AF271156,      71 TGGGCCAGATC
                  ***********

--------------------------------------------------------------------------------
100.0% identity in 11 residues overlap; Score: 11.0; Gap frequency: 0.0%

US692_SEQ_    148 TGGGCCAGATC
AF271156,     149 TGGGCCAGATC
                  ***********

--------------------------------------------------------------------------------81.2%
identity in 16 residues overlap; Score: 10.0; Gap frequency: 0.0%

US692_SEQ_     16 CGGGCGGAGGAGGCGC
AF271156,     159 CGGCCGGAGCAAGCGC
                  *** ***** * ****

--------------------------------------------------------------------------------72.7%
identity in 22 residues overlap; Score: 10.0; Gap frequency: 0.0%

US692_SEQ_    340 GTTAAGGGAGAGAATAGGAACG
AF271156,     178 GTTATTGAAGATGATAGGATCG
                  ****  * ***  ****** **

--------------------------------------------------------------------------------84.6%
identity in 13 residues overlap; Score: 9.0; Gap frequency: 0.0%

US692_SEQ_    131 CGGCGACGGCGGC
AF271156,      63 CGGCGACGTGGGC
                  ********  ***

--------------------------------------------------------------------------------84.6%
identity in 13 residues overlap; Score: 9.0; Gap frequency: 0.0%

US692_SEQ_    140 CGGCGACGTGGGC
AF271156,      54 CGGCGACGGCGGC
                  ********  ***

--------------------------------------------------------------------------------73.7%
identity in 19 residues overlap; Score: 9.0; Gap frequency: 0.0%

US692_SEQ_    394 GAGAAAGCACTTTGAAATT
AF271156,     165 GAGCAAGCGCGTTGTTATT
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                *** **** * ***  ***

-------------------------------------------------------------------------------90.9%
Identity in 11 residues overlap; Score: 9.0; Gap frequency: 0.0%

US692_SEQ_    463 GCCCGGAGACA
AF271156,     399 GCCGGGAGACA
                  *** *******

-------------------------------------------------------------------------------84.6%
Identity in 13 residues overlap; Score: 9.0; Gap frequency: 0.0%

US692_SEQ_    675 AAGCCCCACCCCA
AF271156,     133 AACCGGCCGCCCA
                  ******* ****

-------------------------------------------------------------------------------73.7%
Identity in 19 residues overlap; Score: 9.0; Gap frequency: 0.0%

US692_SEQ_     48 GGCGGAGGAGGCGCCGCGG
AF271156,      55 GCCGACGCCGGCGACGTCC
                  **** ** **** ** **

-------------------------------------------------------------------------------90.9%
Identity in 11 residues overlap; Score: 9.0; Gap frequency: 0.0%

US692_SEQ_    909 AACAAGAAGAG
AF271156,     278 AATAAGAAGAG
                  ** *********

-------------------------------------------------------------------------------84.6%
Identity in 13 residues overlap; Score: 9.0; Gap frequency: 0.0%

US692_SEQ_    881 CTTTAGAAGTTAT
AF271156,     337 CTTTGGAATTTAT
                  **** *** ****

-------------------------------------------------------------------------------80.0%
Identity in 15 residues overlap; Score: 9.0; Gap frequency: 0.0%

US692_SEQ_    200 CGGGCAGAACAAGCG
AF271156,     159 CGGCCGGAGCAACCG
                  *** * ** ******

-------------------------------------------------------------------------------84.6%
Identity in 13 residues overlap; Score: 9.0; Gap frequency: 0.0%

US692_SEQ_    486 GAGGAAGAGAGAG
AF271156,     322 GAGGAGGAGAAAG
                  ***** **** **

-------------------------------------------------------------------------------80.0%
Identity in 15 residues overlap; Score: 9.0; Gap frequency: 0.0%

US692_SEQ_     46 CGGGCGGAGGAGGCG
AF271156,     123 CGGGCAGAGCAAGCG
                  ***** *** * ***
```